

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 99/03267

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WARMAN M L ET AL: "Physical and linkage mapping of the human and murine genes for the alpha 1 chain of type IX collagen (COL9A1)."</p> <p>GENOMICS, (1993 SEP) 17 (3) 694-8. , XP000867629</p> <p>the whole document</p> <p>---</p>	11,15-17
X	<p>WRIGHT G D ET AL: "Association of two loci on chromosome 2q with nodal osteoarthritis--."</p> <p>ANNALS OF THE RHEUMATIC DISEASES, (1996 MAY) 55 (5) 317-9. , XP000867573</p> <p>cited in the application</p> <p>the whole document</p> <p>---</p> <p>-/--</p>	11,16

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

8 February 2000

Date of mailing of the international search report

21/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Reuter, U

# INTERNATIONAL SEARCH REPORT

International Application No

GB 99/03267

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LEPPAVUORI: "Genome scan for predisposing loci of distal interphalangeal joint osteoarthritis" AMERICAN JOURNAL OF HUMAN GENETICS, vol. 63, no. SUPPL., 1998, page a1715 XP000867562 cited in the application the whole document ---	1-18
A	DOHERTY M: "Genetics of osteoarthritis (OA)." SCHWEIZERISCHE MEDIZINISCHE WOCHENSCHRIFT. SUPPLEMENTUM, (1996) 80 6S-7S., XP000867748 the whole document ---	1-18
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A	US 5 691 153 A (GONG GUODONG ET AL) 25 November 1997 (1997-11-25) the whole document ---	1-18
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>AHB/LP5799374</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 99/ 03267</b>	International filing date (day/month/year) <b>04/10/1999</b>	(Earliest) Priority Date (day/month/year) <b>02/10/1998</b>
Applicant  <b>CATALYST BIOMEDICA LTD. et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**SUSCEPTIBILITY LOCUS FOR OSTEOARTHRITIS**

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

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☒ Further documents are listed in the continuation of box C.

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### \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search

8 February 2000

Date of mailing of the international search report

21/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/03267

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5558988	A	24-09-1996	WO	9411532 A	26-05-1994
			US	5948611 A	07-09-1999
WO 9740187	A	30-10-1997	AU	2395697 A	12-11-1997
			CA	2251744 A	30-10-1997
			EP	0909330 A	21-04-1999
			US	5939260 A	17-08-1999
US 5691153	A	25-11-1997	NONE		

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
 United States Patent and Trademark  
 Office  
 Box PCT  
 Washington, D.C.20231  
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 11 May 2000 (11.05.00)	
<b>International application No.</b> PCT/GB99/03267	<b>Applicant's or agent's file reference</b> AHB/LP5799374
<b>International filing date</b> (day/month/year) 04 October 1999 (04.10.99)	<b>Priority date</b> (day/month/year) 02 October 1998 (02.10.98)
<b>Applicant</b> SYKES, Bryan et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

14 April 2000 (14.04.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Juan Cruz

Telephone No.: (41-22) 338.83.38



# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/03267

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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
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Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

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PCT/GB 99/03267

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Information on patent family members

International Application No

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WO 9740187	A	30-10-1997	AU	2395697 A	12-11-1997
			CA	2251744 A	30-10-1997
			EP	0909330 A	21-04-1999
			US	5939260 A	17-08-1999
US 5691153	A	25-11-1997	NONE		

## PATENT COOPERATION TREATY

## PCT


REC'D 22 DEC 2000

WIPO

PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference AHB/LP5799374		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB99/03267	International filing date (day/month/year) 04/10/1999	Priority date (day/month/year) 02/10/1998	
International Patent Classification (IPC) or national classification and IPC C12Q1/68			
Applicant CATALYST BIOMEDICA LTD. et al.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 10 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"><li>I <input checked="" type="checkbox"/> Basis of the report</li><li>II <input type="checkbox"/> Priority</li><li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li><li>IV <input checked="" type="checkbox"/> Lack of unity of invention</li><li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li><li>VI <input type="checkbox"/> Certain documents cited</li><li>VII <input type="checkbox"/> Certain defects in the international application</li><li>VIII <input checked="" type="checkbox"/> Certain observations on the international application</li></ul>			
Date of submission of the demand  14/04/2000		Date of completion of this report  19.12.2000	
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer  Barz, W  Telephone No. +49 89 2399 7320	



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/03267

**I. Basis of the report**

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

**Description, pages:**

1-28 as originally filed

**Claims, No.:**

1-18 as originally filed

**Drawings, sheets:**

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03267

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

### III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-3, 11, 13 (IA).

because:

☒ the said international application, or the said claims Nos. 1-3, 11, 13 (IA) relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

### IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/03267

- ☐ paid additional fees.
- ☐ paid additional fees under protest.
- ☒ neither restricted nor paid additional fees.
- 2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
- 3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
  - ☐ complied with.
  - ☒ not complied with for the following reasons:  
**see separate sheet**
- 4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
  - ☐ all parts.
  - ☒ the parts relating to claims Nos. 1-10, 11 (partially), 12-13, 16 (partially), 18.

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims	1-10, 11 (partially), 12-13, 16 (partially), 18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-10, 11 (partially), 12-13, 16 (partially), 18
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	4-10, 12, 16 (partially), 18
	No:	Claims	

### 2. Citations and explanations **see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB99/03267

Reference is made to the following documents:

- D1: GENOMICS (Warman M.L. et al.), 17 (1993) 694-698;
- D2: ANNALS OF THE RHEUMATIC DISEASES, 55 (1996) 317-319,  
(Wright G.D. et al.), cited in the application;
- D3: AMERICAN JOURNAL OF HUMAN GENETICS, 65 (1999) 167-74,  
(Chapman, K. et al.);
- D4: JOURNAL OF MEDICAL GENETICS, 36 (1999), Suppl. 1, S25,  
(Loughlin, J. et al.); MEETING INFO.: CONFERENCE ON BRITISH  
HUMAN GENETICS YORK, ENGLAND, SEPTEMBER 27-29, 1999.

**ITEM III:**

Due to the expression "obtaining a sample of genomic DNA", **claims 1-3, 11 and 13** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT). See, however, item V-3. below.

**ITEM IV:**

1. For the following reasons, the independent claims of the present application are not so linked as to form a single general inventive concept (Rule 13.1 PCT):
  - 1.1 The common concept linking together the various alternatives encompassed by the independent claims 1, 4, 5, 7, 10, 11, 16, and 18 can be formulated as the provision of linkages between the susceptibility to osteoarthritis and chromosomal loci as identified by polymorphic markers.
  - 1.2 However, this concept cannot be considered as novel and inventive, because the following documents report the identification of gene polymorphisms which are linked to increased susceptibility to osteoarthritis.



D1 discloses the identification of two highly polymorphic short tandem repeat polymorphisms in the human COL9A1 gene (coding for the  $\alpha 1$  chain of type IX collagen) which has been mapped to chromosome 6q12-13 (abstract; page 694, right column, lines 7-13). Furthermore, D1 suggests the use of said polymorphisms for studying genetic disorders such as osteoarthritis (page 697, lines 22-30).

According to document D2, two microsatellite marker loci on chromosome 2q (2q23-25 and 2q33-35) are genetically linked to osteoarthritis, thus pointing to the presence of genes in this region which might be involved in the pathogenesis of said disease (abstract; page 318, right column, lines 22-26).

- 1.3 Both documents suggest the further investigation of said chromosomal regions for the identification of the linkage sites and the genes located therein.
2. Consequently, the concept of genetic linkages between the susceptibility to osteoarthritis and chromosomal loci as identified by polymorphic markers is already known from the prior art. The requisite unity of invention (Rule 13.1 PCT) therefore no longer exists inasmuch as a technical relationship involving a special technical features in the sense of Rule 13.2 PCT does not exist between the following separate groups of inventions:
  1. Linkage of enhanced susceptibility to osteoarthritis with a genetic locus on chromosome 11 (claims 1-10, 11 partially, 12-13, 16 partially, and 18).
  2. Linkage of enhanced susceptibility to osteoarthritis with genetic loci on chromosome 2 (claims 11 partially and 16 partially).
  3. Linkage of enhanced susceptibility to osteoarthritis with genetic loci on chromosome 3 (claims 11 partially and 16 partially).

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4. Linkage of enhanced susceptibility to osteoarthritis with genetic loci on chromosome 4 (claims 11 partially and 16 partially).
  5. Linkage of enhanced susceptibility to osteoarthritis with genetic loci on chromosome 6 (claims 11 partially, 14-15, 16 partially, and 17).
  6. Linkage of enhanced susceptibility to osteoarthritis with genetic loci on chromosome 7 (claims 11 partially and 16 partially).
  7. Linkage of enhanced susceptibility to osteoarthritis with genetic loci on chromosome 17 (claims 11 partially and 16 partially).
  8. Linkage of enhanced susceptibility to osteoarthritis with genetic loci on chromosome X (claims 11 partially, 14-15, 16 partially, and 17).
3. Upon invitation pursuant to Article 34(3)(a) and Rule 68.2 PCT, the applicant did not pay additional fees and requested that the international examination should proceed on the basis of first group of inventions (claims 1-10, 11 partially, 12-13, 16 partially, and 18).

**ITEM V:**

1. NOVELTY

The present application meets the requirements of Article 33(2) PCT, because none of the available prior art documents discloses the association of a genetic locus on chromosome 11 with enhanced susceptibility to osteoarthritis. Therefore, the subject-matter of **claims 1-13, 16, and 18** (as far as they refer to chromosome 11) is novel.

## 2. INVENTIVE STEP

Similarly, the present application appears to meet the requirements of Article 33(3) PCT, because the subject-matter of **claims 1-13, 16, and 18** (as far as they refer to chromosome 11) seems to involve an inventive step for the following reasons.

- 2.1 Document D2, which is considered to represent the closest prior art, discloses two microsatellite marker loci on chromosome 2q (2q23-25 and 2q33-35) which are genetically linked to osteoarthritis (abstract; page 318, right column, lines 22-26). Compared to D2, the methods of the present application (as far as they refer to chromosome 11) differ by the fact that the genomic locus associated with enhanced susceptibility to osteoarthritis are located on chromosome 11.
- 2.2 The technical problems to be solved by the present invention may therefore be regarded as how to provide methods for identifying individuals susceptible to osteoarthritis and methods for isolating or identifying genetic loci associated with susceptibility to osteoarthritis, wherein these methods are based on polymorphic markers on chromosome 11 (such as the "258 bp allele" of D11S937; see however item VIII-1. below).
- 2.3 Since the available prior art neither discloses nor suggests the association of enhanced susceptibility to osteoarthritis with a genetic locus on chromosome 11, the subject-matter of **claims 1-13, 16, and 18** (as far as they refer to chromosome 11) appears to be inventive in the sense of Article 33(3) PCT.

## 3. INDUSTRIAL APPLICABILITY

- 3.1 For the assessment of the present **claims 1-3, 11 and 13** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the treatment of the human or animal body by surgery.

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- 3.2 Concerning the applicant's arguments provided with the letter dated 07 November 2000, the International Preliminary Examining Authority agrees that the expression "obtaining a sample of genomic DNA" comprises methods which are not practised on the human or animal body. Since, however, surgical methods of obtaining a DNA sample are also comprised in the said expression, the International Preliminary Examining Authority maintains its objection under Rule 67.1(iv) PCT (see item III above).

4. P-DOCUMENTS

The present application claims priority from four documents (three having the application date 02 October 1998 and one having the application date on 15 February 1999). Since the priority is validly claimed for the patent application dated 15 February 1999, the prior art documents D3 and D4 which were published after that date, but before the filing date of the present application (listed as "P,X" documents in the International Search Report) are not relevant for the present application.

**ITEM VIII:**

1. **Claim 4** does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. Both terms "screening a genomic library [...]" and "identifying ORFs [...]" do not specify how the screening and identification is performed and thus do not enable the skilled person to determine which technical features are necessary for these steps. Consequently, the claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem.

Concerning the applicant's argument provided with the letter dated 07 November 2000, the International Preliminary Examining Authority does not agree with the statement that claim 4 provides a sequence with which to screen a library. The fact that claim 4 defines the individual (from which the library to be screened is

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constructed) to be "homozygote for the 258 bp allele of D11S937" does not instruct the skilled person to use this allele for screening the library. Consequently, claim 4 is not clear in the sense of Article 6 PCT.

2. **Claims 12-13** refer to the method for determining individual osteoarthritis susceptibility "according to claim 10", although claim 10 does mention such a method.